

## ORIGINAL ARTICLE

## Characteristics of adenovirus associated urethritis

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**Objectives:** To describe the characteristics of adenovirus urethritis in men.

**Method:** Cases occurred over a 30 month period among men presenting with urethritis to Melbourne Sexual Health Clinic. All cases had a urethral Gram stain and underwent testing for chlamydia, gonorrhoea, herpes, and adenovirus. Cases were empirically treated with a macrolide or doxycycline.

**Results:** Eight cases of adenovirus associated urethritis were identified in whom no other causative organism was isolated. Cases were clustered in autumn and winter of each year and all reported recent insertive oral sex and seven reported recent insertive vaginal sex. All patients complained of dysuria, seven had meatitis and mucoid discharge, six had conjunctivitis, and four constitutional symptoms. Three sexual contacts were known to be symptomatic.

**Conclusion:** Adenovirus is an uncommon cause of urethritis in men but it should be considered in all males presenting with dysuria, meatitis, and associated conjunctivitis or constitutional symptoms.

Non-specific urethritis (NSU) is a common presentation to sexual health clinics and in a substantial proportion of cases no pathogen is identified. There are few reports of adenovirus associated with urethritis in men, and it is not usually considered when investigating NSU.

Adenovirus causes a variety of clinical syndromes characterised by inflammation of mucous membranes. There are 47 serotypes; types 8, 19, and 37 (subgenus D) cause keratoconjunctivitis,<sup>1-6</sup> but have also been infrequently isolated from genital sites in individuals with cervicitis,<sup>3-8</sup> urethritis,<sup>5, 6, 9, 10</sup> and genital ulcers.<sup>6, 7</sup> We describe characteristic clinical features in eight men presenting with urethritis to a sexual health clinic in whom adenovirus appears to have been the causative agent.

## METHOD

All eight cases were collected between April 1999 and September 2001 at Melbourne Sexual Health Centre (MSHC). MSHC services a city of 3.5 million people and sees approximately 15 000 new patients per annum. Adenovirus was tested for in men presenting with urethritis in addition to meatitis or conjunctivitis. Routine screening of all men with urethritis was not performed.

A urethral Gram stain was performed on all cases. Chlamydia testing was by ligase chain reaction (LCR, Abbott LCR probe system) on a first void urine specimen. Gonococcal testing was performed by culture on gonococcal medium at MSHC. Herpes was excluded by in-house nested polymerase chain reaction (PCR) at the Victorian Infectious Diseases Reference Laboratory (VIDRL). Adenovirus was isolated using viral culture, with confirmation by antibody neutralisation, and in-house nested PCR<sup>11</sup> by VIDRL and four isolates were serotyped by neutralisation assay. HIV 1 and 2 testing was by enzyme immunoassay (Abbott HIV1/2 Go EIA) at VIDRL.

## RESULTS

All eight cases that tested positive were suspected clinically of having adenovirus. Cases were clustered between April and September each year, corresponding to the seasons of autumn to winter in Melbourne. Seven men were identified as heterosexual, one as homosexual, and the mean age was 36.4 (table 1).

All eight cases reported a recent history of insertive oral sex (IOS), with six reporting IOS in the 14 days preceding onset of

symptoms. Six males reported unprotected vaginal intercourse (UPVI) in the preceding 14 days. Sexual partners were Australian residents except for two Thai partners in Thailand.

All patients complained of marked dysuria, seven had a mucoid urethral discharge and seven had meatitis. Conjunctivitis was present in six cases, constitutional symptoms in four, and pharyngitis was present in one. Three sexual contacts were known to be symptomatic: two females had conjunctivitis, with additional cervicitis in one, and one male contact had dysuria and pharyngitis.

Urethral Gram stain revealed more than four polymorphonuclear cells (PMN) per high powered field in six cases. A further case had no PMNs on initial presentation, but developed a florid discharge subsequently and was not retested. Another had 1-4 PMNs on Gram stain. Cases were considered positive for adenovirus if samples tested positive by culture or PCR (table 1). Adenovirus was identified in all urethral swabs and in the four conjunctival swabs collected. Typing was performed for four urethral isolates; three cases were type 37 and one was type 8. Typing was not performed for specimens tested by PCR alone and was not requested in all patients tested by culture. All patients received empirical treatment for NSU with either doxycycline or azithromycin, and two received additional famciclovir. No case tested positive for chlamydia, gonorrhoea, or herpes. Six cases were tested for HIV and were negative. Five cases had symptoms persisting for 14 days or more despite antibiotic therapy.

## DISCUSSION

We have described eight cases where adenovirus was isolated in men presenting with NSU associated with marked dysuria, meatitis, and conjunctivitis. There were strong similarities in the clinical presentations of the cases. Oral sex preceded the onset of symptoms in all cases and vaginal sex was a common exposure. There was seasonal clustering of cases in autumn and winter each year. The four isolates typed were of subgenus D (types 8 and 37), an established cause of keratoconjunctivitis.<sup>1-6</sup>

Testing was not performed for *Trichomonas vaginalis* given the low prevalence in the population attending our clinic, or for *Ureaplasma urealyticum* because of high rates of asymptomatic urethral colonisation. Testing was not performed for *Mycoplasma genitalium* as PCR is required and is not routinely available in most clinic settings. *U. urealyticum* and *M. genitalium*

**Table 1** Clinical and laboratory findings

Case	Age	Season	Sexual history	Genital symptoms and signs	Associated symptoms	Contact symptoms & signs	Urethral PMN count	Urethral isolate	Conjunctival isolate	Treatment
1	28	Winter 1999	IOS and PVI with CSPs 18 and 7 days before onset of D	Severe D, MUD, and MT, resolved by day 22	CNJ and CS	Unknown	0	Ad 37†	NT	Doxy and famv
2	20	Winter 1999	IOS and UPVI with RSP—regular sexual activity but no dates of contact documented	Severe D, MUD, and MT, ongoing day 14	CS	CNJ and cervicitis (chl and gon negative)	8–20	Ad†	NT	Doxy and famv
3	44	Autumn 2000	IOS and UPVI with RSP 3 days before onset of D	Severe D, MUD, and MT, resolved by day 18	CNJ and CS	Well	8–20	Ad 37††	Ad††	Doxy and roxi
4	35	Autumn 2000	IOS and UPVI with CSP in Thailand 9 days before onset of D	D and MT, ongoing day 5	CNJ and CS	Unknown	5–8	Ad††	Ad††	azith
5	33	Autumn 2000	IOS and UPVI with a CSP 14 days before onset of D	D and MUD (altered urinary stream), resolution by day 14	CNJ	CNJ	1–4	Ad 37††	NT	azith
6	47	Winter 2001	IOS and UPVI with CSP 6 days before onset of D	Severe D, MUD, and MT, ongoing d5	Nil	Unknown	8–20	Ad 8††	NT	azith
7*	35	Winter 2001	IOS with RSP 10 days before D, IOS and IAS with CSP 28 days before onset of D	D, MUD, and MT, ongoing d15	CNJ and pharyngitis	RSP had D and pharyngitis (recent chl treated)	8–20	Ad†	Ad†	azith
8	49	Winter 2001	IOS and UPVI with RSP in Thailand—regular sex but no dates specified	Severe D, MUD, and MT, present for >9 days	CNJ	Unknown	5–8	Ad†	Ad†	azith, doxy, and roxi

\*Homosexual, all other cases heterosexual. Insertive oral sex (IOS), vaginal intercourse (VI), condom used (PI), unprotected (UPI), regular sexual partner (RSP), casual sexual partner (CSP), dysuria (D), mucoid urethral discharge (MUD), meatitis (MT), conjunctivitis (CNJ), constitutional symptoms (CS), polymorphonuclear cells per high power field (urethral PMN count), chlamydia (chl), gonorrhoea (gon), adenovirus (Ad), adenovirus type 37 (Ad37), culture positive (†), PCR positive (††), not tested (NT), azithromycin (azith), doxycycline (doxy), roxithromycin (roxi), and famciclovir (famv).

have no established association with conjunctivitis or constitutional symptoms and are usually sensitive to the antimicrobial therapy prescribed in our cases. We did not screen all men presenting with urethritis for adenovirus, instead testing only those with associated conjunctivitis or meatitis. These features were uncommon, and all individuals presenting with urethritis and meatitis or conjunctivitis tested positive in the present study. This series may represent only a proportion all adenovirus infections presenting over this period.

It is significant that cases followed a history of oral sex, an important risk factor for NSU in which the microbial agent is unknown. Adenovirus has also been shown to infect the female genital tract and has been isolated in women with labial ulcers,<sup>6</sup> vulvo-vaginitis,<sup>7</sup> and cervicitis.<sup>5–8</sup> Sexual transmission appears to be the most plausible mode of acquisition of urethral infection, either through insertive oral or possibly vaginal sex. Conjunctivitis may have occurred through autoinoculation or be related to sexual activity. The characteristic clinical and epidemiological features, the failure to respond rapidly to antibiotic treatment, and the isolation of adenovirus from the urethra, all support adenovirus as a cause of urethritis in these cases.

Studies regarding the prevalence and role of adenovirus as a causative agent of urethritis are limited. Subgenus D adenoviruses, in particular, have been shown to manifest an affinity for the eye and genital tract.<sup>12</sup> Harnett *et al* screened 35 800 men and isolated adenovirus from the urethral swabs of 0.36%; 71% had urethritis and 14% had conjunctivitis. The majority of isolates were serotypes 19 or 37 and outbreaks coincided with epidemics of conjunctivitis in the community. Swenson *et al* screened symptomatic patients in the United States with genital ulcers, urethritis, or conjunctivitis,<sup>6</sup> and isolated adenovirus from 0.33% of men. Urethritis was present in 75%, conjunctivitis in 60%, and 50% had both. All three female cases had vaginal discharge and genital ulcers. The majority of specimens were type 37 and two were type 8. As in our series there was a strong association with conjunctivitis and urethritis. A case series from New Zealand of six symptomatic men with adenovirus associated urethritis resembled our series in the severity of dysuria, history of insertive oral sex, presence of either constitutional symptoms or conjunctivitis, and suboptimal response to antimicrobial therapy.<sup>10</sup> However, no seasonal association was seen, five of six cases were homosexual, and serotyping was complicated by cross reaction.

Although an uncommon cause of urethritis, adenoviruses, particularly types 8 and 37, appear to cause a distinct and recognisable clinical syndrome in men presenting with NSU. Oral sex appears to be a risk factor and presentation may be seasonally related. The presence of marked dysuria, meatitis, conjunctivitis, and constitutional symptoms should alert all physicians to adenovirus as a possible causative organism in NSU.

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## CONTRIBUTORS

CB initiated the study, collected cases and was principal investigator; ID collected cases and all three authors contributed to data interpretation and the drafting of the paper.

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## WEBSITE REVIEW .....

### [www.chlamydiae.com](http://www.chlamydiae.com)

This is arguably the most comprehensive medical website to host information on chlamydial infections. It is set up and designed by Michael Ward, professor of medical microbiology at the University of Southampton. The site boasts not only a multilingual (12 languages) textbook on chlamydiae but also a calendar of relevant scientific meetings, conference, and news reports. The web caters for health professionals as well as the general public and covers factual information in the form of FAQs focused on genital tract infections.

Only about half of the “health professionals” area requires (free of charge) registration initially for log-in (albeit that section of most interest to *STI* readers), but the wealth of accurate and up to date information contained within should make this site a compelling reason for putting it on your list of websites to be bookmarked. Excellent.

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